FIGHT MND.


A/Prof Anna King

Researcher.
A/PROF ANNA KING

Drug Development Project.
HDAC6 INHIBITION TO RESCUE AXON DEGENERATION IN ALS

Where do you work?

I work at the Wicking Dementia Research and Education Centre which is part of the College of Health and Medicine at the University of Tasmania.

Can you give us a summary of your research experience and background?

I undertook an honours degree in Molecular Biology and Biochemistry at the University of Durham (UK) and further trained in molecular techniques at the Heart Research Institute in Sydney. I obtained my PhD in neuroscience at the University of Tasmania, where I first developed and interest in MND research and learned to work with animal and cell culture models. My postdoctoral fellowships were funded by the Motor Neuron Disease Research Institute of Australia and Dementia Australia Research Foundation, and these enabled me to begin to develop my own research program at the Wicking Dementia Centre, seeking to identify neuroprotective strategies for disease and injury. In 2017 I took on the role of Associate Director (Research) for the Wicking Centre and was awarded a Dementia Leadership Fellowship from the NHMRC to investigate blood biomarkers of neurodegeneration.

Why did you decide to pursue MND research?

I have been studying MND since the start of my PhD in 2004 and my PhD scholarship was funded by the Rotary Club of Deloraine to work in this field. I knew little about MND at the beginning of my PhD, but I joined a research team who are driven to understand the pathology of neurodegenerative disease, including MND. Since this time, I have been inspired to continue this research through realisation of the desperate need to find a cure for MND and through interaction with patients, clinicians and the research community.

Can you describe the current focus of your research team?

The focus of our research team is to develop therapeutic strategies to protect a part of the nerve cell called the axon. The axon is like an electrical cable that transfers signals from one nerve cell to another and these structures can be extremely long (over 1 metre in humans), making them very vulnerable to degeneration. Axons have independent mechanisms of degeneration and may need to be targeted to maintain the signalling between neurons and muscle cells. We have evidence that stabilising a type of structural protein in axons, called microtubules, may help protect axons, and we want to test if this helps prevent some of the clinical symptoms of MND either when used alone or in combination with other treatments. Part of our research is also to develop ways of detecting when axon damage is occurring in the nervous system through measuring proteins in the blood. This will enable prognosis and diagnosis of neurodegenerative disease and injury.

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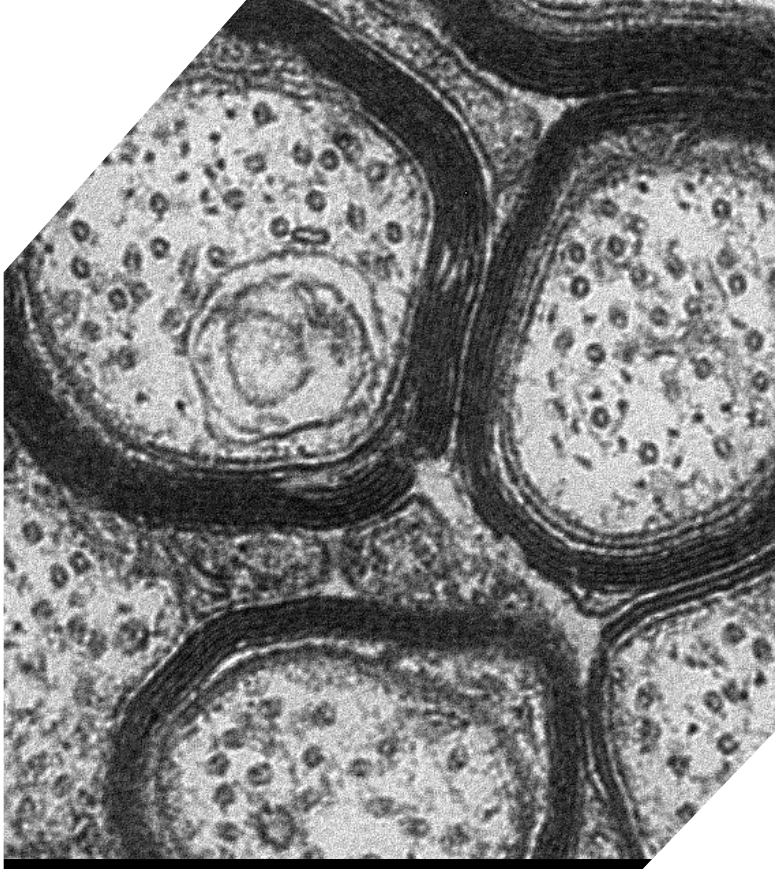

Electron micrograph of a cross section of the optic nerve. Axons seen are surrounded by a dark fatty substance called myelin. Within the axons, structural components can be seen, including ring-like microtubules proteins.

What has been your most surprising finding?

This is not really a finding, but one of the most amazing things that I have seen in the laboratory is the contraction of muscle cells growing in a dish. We used cell culture techniques and microfluidic technology to develop a model of the neuromuscular junction, which is the point where the motor neuron axon contacts the muscle cell, causing it to contract. In our model, we grew spinal motor neurons in a dish and directed their axons to innervate primary muscle cells. Over time, the muscle cells developed the ability to spontaneously contract, just like the contractions of muscle cells in our body.

What excites you about HDAC6 inhibitors?

Over the past few years there have been an increasing number of studies suggesting that stabilising microtubules may have protective effects on neurons. I think the exciting thing about HDAC6 inhibitors is that they work with the neurons normal processes to stabilise microtubules rather than adding extrinsic stabilising molecules. HDAC6 inhibitors work by increasing the acetylation of microtubules, which is a more stable microtubule form. These drugs may also have other beneficial effects in the nervous system, such as modulation of protein degradation pathways and inflammation.

What will this funding allow your team to do?

This research funding has given us a fantastic opportunity to form an international collaboration and to bring together a team from across multiple disciplines to work together to advance our understanding of this target and its ability to maintain these vital connections between nerve cells. Not only will we be able to test HDAC6 inhibitors in multiple animal models of MND, we will also be able to test these drugs in human cells (induced pluripotent stem cells) and to work with chemists, pharmacists and clinicians to further develop these drugs to improve their use as therapeutics.

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Loss of movement in MND results from degeneration of the nerve cell processes, which are responsible for transmitting signals to the muscles. In preclinical MND models, protecting nerve cells, but not the nerve cell processes, fails to restore motor function. Therefore, protection of nerve cell processes needs to be considered when developing therapeutics aimed at treating MND.

We have identified a class of drugs, known as HDAC6 inhibitors, that may protect nerve cell process in MND. Normally, the enzyme HDAC6 maintains the structure of motor neurons, but in MND, HDAC6 becomes damaging to motor neurons, leading to their degeneration and failed communication with muscles. In our cell models of MND, HDAC6 inhibitors prevent the degeneration of nerve cell processes and rescue their function. These drugs also have other positive effects on cell health, which will be beneficial for MND. One drug in particular can access the brain and our aim is to determine if this class of drugs can rescue nerve cell processes in preclinical models of MND.

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OBJECTIVES:

- Test if specific HDAC6 inhibitor drugs protect nerve cell processes and rescue communication between nerve cells and muscles in 4 preclinical MND/ALS models, and a human cell model of sporadic MND.
- Screen over 150 compounds we have developed for their ability to inhibit HDAC6 using mouse-derived cortical neurons. If a new drug candidate is identified, we will determine if it can enter the brain and if it is a better drug for clinical development. To do this, we have brought together an international team which includes research experts in MND, chemists, pharmacists and clinicians.

OUTCOMES:

- Establish if HDAC6 inhibitors prevent degeneration of nerve cells and their processes and slow disease progression in 4 preclinical MND models and a human cell model of MND.
- Proof of concept that HDAC6 inhibitors are promising for treating MND.
- Identification of novel HDAC6 inhibiting drugs to advance treatment of MND.